REMARKS/ARGUMENTS

Claims 1 to 21 and 35 to 47 are pending. Applicant has canceled claims 22 to 34 in response to a restriction requirement without prejudice to pursuing these claims in a continuing application. Applicant has added new dependent claims 35 to 47. The new claims find full support in the original specification at, for example, page 9, lines 9 to 31, and page 14, lines 4 to 22. No new matter is presented. In view of the above amendments and following remarks, Applicant respectfully requests favorable reconsideration and a timely indication of allowance.

As an initial matter, neither the present Office action or the previous Office action indicated whether the drawings are accepted by the Examiner. Applicant respectfully requests that the Examiner provide with the next action an indication as to whether the drawings are acceptable.

Additionally, the domestic priority data listed on the filing receipt for this application does not match the priority data provided by Applicant. Applicant recognizes that the Patent Office has had difficulty in prior related applications getting a corrected filing receipt that correctly lists the priority data, and it was necessary for Applicant to seek the Examiner's assistance Applicant again requests the Examiner's assistance in assuring that the Office's file contains a correct listing of the priority data for this application so that the correct information will appear on any patent to issue from this application.

The Examiner rejected claims 1, 2, 4 to 7, 15 to 18, 20 and 21 under 35 U.S.C. § 102(b) as allegedly anticipated by Diminsky (New Generation of Vaccines, 1993). Applicant respectfully traverses this rejection.

The Examiner states that Diminsky teaches lyophilizes liposomes containing hepatitis antigen for use as a vaccine. The Examiner states that, because Applicant's claims do not recite any percentages of specific populations of liposomes based on size, the burden is on Applicant to show that the lyophilized liposomes are different from Diminsky's liposomes. As Applicant understands the Examiner's position, he is contending that Diminsky inherently discloses liposomes having at least two sizes, before lyophilization, selected from small liposomes having a size, before lyophilization, of from about 20 nm to about 1 micron, medium liposomes having a size, before lyophilization, of from about 1 micron to about 3 microns, and large liposomes having a size, before lyophilization, of from about 3 microns to about 20 microns, as recited in claim 1.

To support an anticipation rejection based on inherency, the Examiner must provide factual and technical grounds establishing that the inherent feature *necessarily* flows from the teachings of the prior art. *In re Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990). Acknowledging that the Examiner does

not have the requisite laboratory equipment for testing, the Board nonetheless emphasized that the initial burden of establishing a *prima facie* basis to deny patentability to a claimed invention rests upon the Examiner. *Id.* at 1463-64.

In the present case, the Examiner has provided absolutely no factual or technical grounds to support that Diminsky's liposomes inherently have at least two sizes, before lyophilization, selected from small liposomes having a size, before lyophilization, of from about 20 nm to about 1 micron, medium liposomes having a size, before lyophilization, of from about 1 micron to about 3 microns, and large liposomes having a size, before lyophilization, of from about 3 microns to about 20 microns, as recited in claim 1. The only liposome size disclosed in Diminisky is at page 56, where Diminsky states that the liposomes had an average size of 4.5 microns. This value falls within Applicant's large liposome size range. Nothing in Diminisky even suggests that some of the liposomes had a size less than about 3 microns.

The present application describes a process for producing liposomes having different sizes as presently claimed. The process involves actively reducing the sizes of the liposomes, for example, by sonication. Nothing in Diminsky suggests that any steps were taken to reduce the sizes of some of the liposomes so that liposomes of different sizes were produced. Thus, Diminisky provides no factual or technical support for the conclusion that his liposomes had two different sizes as presently claimed. Accordingly, the Examiner has not established a *prima facie* case of inherency with respect to Diminisky. Applicant therefore respectfully requests that the rejection under section 102(b) over Diminsky be withdrawn.

The Examiner rejected claims 1, 2 4 to 7 and 10 to 21 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sato et al. (U.S. Patent No. 5,573,779) or Aramaki (Pharmaceutical Research 1993) in view of Diminsky, and optionally further in view of Gregoriadis (Liposomes as Drug Carriers 1988). Applicant respectfully traverses this rejection.

In making this rejection, the Examiner did not address the claim limitation requiring liposomes having at least two different sizes. In fact, this limitation is not taught by any of the references. As discussed above, Diminsky does not teach, suggest or inherently disclose the different sized liposomes of the present invention.

Sato is directed to a liposome composition for targeting Peyer's patches. Sato does not provide a teaching of a specific desired liposome size, much less a teaching or suggestion to use liposomes of different sizes, as presently claimed. Sato states that the liposomes can be prepared by any suitable method, and that liposomes having the desired particle size can be obtained by filtering a prepared liposome solution. (See

column 3, lines 42 to 65.) But Sato provides absolutely no guidance as to what that desired particular size might be, much less to create different sizes.

Aramaki is directed to evaluating the usefulness of liposomes as carriers for the targeted delivery of antigens to gut-associated lymphoid tissue. As part of this evaluation, Aramaki creates a number of liposomal preparations, each having a different liposome size, namely, 162 nm, 374 nm and 855 nm, all of which fall within Applicant's small liposome size range. (See page 1230, Fig. 3.) Aramaki concludes that liposomes of large size (374 and 855 nm) were preferentially taken up by Peyer's patches. (See page 1231.) However, Aramaki does not teach or suggest using liposomes of different sizes, as presently claimed.

Gregoriadis is cited for teaching that lyophilization is routinely practiced in the art. However, Gregoriadis provides no teaching of desirable sizes of liposomes for oral administration to target the Peyer's patches, much less using different sizes as presently claimed.

Accordingly, none of the cited references teaches or suggests using liposomes of different sizes as presently claimed. Therefore, even in combination, the cited references to not render unpatentable claim 1 or any claim depending therefrom, and Applicant requests that this rejection be withdrawn.

The Examiner rejected claim 3 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sato or Aramaki in view of Diminsky, and optionally in view of Gregoriadis, and further in view of Geary et al. (U.S. Patent No. 5,382,435). Applicant respectfully traverses this rejection.

As discussed above, none of Sato, Aramaki, Diminsky or Gregoriadis teaches or suggests using liposomes of different sizes, as presently claimed. Geary does not remedy this deficiency. Geary is cited to disclose an enteric coating for liposomes. However, Geary's disclosure focuses on the coating and does not address the size of the liposomes being coated. Geary nowhere teaches or suggests using liposomes of different sizes, as presently claimed. Applicant therefore respectfully requests that this rejection be withdrawn.

The Examiner rejected claims 15 and 19 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sato or Aramaki in view of Diminsky, and optionally in view of Gregoriadis, and further in view of Fullerton. (U.S. Patent No. 4,199,565). Applicant respectfully traverses this rejection.

As discussed above, none of Sato, Aramaki, Diminsky or Gregoriadis teaches or suggests using liposomes of different sizes, as presently claimed. Fullerton does not remedy this deficiency. Fullerton is cited to disclose hepatitis and influenze viruses. Fullerton nowhere teaches or suggests any desirable

liposome sizes, much less using liposomes of different sizes, as presently claimed. Applicant therefore respectfully requests that this rejection be withdrawn.

The Examiner rejected claim 11 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sato or Aramaki in view of Diminsky, and optionally in view of Gregoriadis, and further in view of Barchfeld et al. (U.S. Patent No. 5,709,879). Applicant respectfully traverses this rejection.

As discussed above, none of Sato, Aramaki, Diminsky or Gregoriadis teaches or suggests using liposomes of different sizes, as presently claimed. Barchfeld does not remedy this deficiency. Barchfeld is cited to teach encapsulation of specific HIV antigens. Barchfeld is directed to a vaccine formulation comprising two components, namely, an antigen/liposome component and an oil-in-water emulsion. In the Background of the Invention, Barchfeld states that liposomes typically vary in size from about 25 nm to about 1 micron. However, Barchfeld provides no teaching about the sizes of the liposomes used in her invention, much less a teaching or suggestion to use two different sizes, as presently claimed. Applicant therefore respectfully requests that this rejection be withdrawn.

New claims 35 to 47 all depend from claim 1, and are therefore allowable over the cited references for the reasons discussed above. Further, new claim 35 recites that the liposomal preparation is prepared by preparing a plurality of liposomes containing the at least one antigen; and reducing the size of a portion of the liposomes to produce liposomes having a size selected from small liposomes and medium liposome, wherein a remainder of the liposomes are not altered so that the remainder of the liposomes have a size selected from medium liposomes and large liposomes, wherein the size of the remainder of the liposomes is different from the reduced size of the portion of liposomes. Remaining claims 36 to 47 include similar limitations. This method is neither taught or suggest by any of the cited references. Accordingly, new claims 35 to 47 are allowable over the cited references for this reason as well.

The Examiner provisionally rejected claims 1 to 21 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 7 and 15 to 34 of U.S. Patent No. 6,015,576. Upon an indication of otherwise allowable subject matter, Applicant will submit an appropriate terminal disclaimer to obviate this rejection.

In view of the foregoing amendments and remarks, Applicant respectfully submits that pending claims 1 to 21 and 35 to 47 are in condition for allowance, and a timely indication of allowance is respectfully requested. If there are any remaining issues that can be addressed by telephone, Applicant invites the Examiner to contact the undersigned at the number indicated below.

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

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